Optimization of IL13Ralpha2-Targeted Chimeric Antigen Receptor T Cells for Improved Anti-tumor Efficacy against Glioblastoma.

Authors: Christine E Brown, Brenda Aguilar, Renate Starr, Xin Yang, Wen-Chung Chang, Lihong Weng, Brenda Chang, Aniee Sarkissian, Alfonso Brito, James F Sanchez, Julie R Ostberg, Massimo D'Apuzzo, Behnam Badie, Michael E Barish, Stephen J Forman

Public Summary:

T cell immunotherapy is emerging as a powerful strategy to treat cancer and may improve outcomes for patients with glioblastoma (GBM). We have developed a chimeric antigen receptor (CAR) T cell immunotherapy targeting GBM cells (specific for IL-13 receptor α2 [IL13Rα2] on the cell surface). Here, we describe the optimization of IL13Rα2-targeted CAR T cells, including improvements in the CAR design and manufacturing platform. Experiments with GBM models created from human tumor cells implanted in mice showed that optimized CAR T cells had improved persistence and anti-tumor activity compared with our first-generation anti-GBM CAR T cells. Given the frequent use of corticosteroids in the clinical management of GBM, we evaluated the impact of corticosteroids on CAR T cells and found that low-dose dexamethasone does not diminish CAR T cell anti-tumor activity in vivo. We also investigated the route of delivery of CAR T cells on efficacy. We found that local intracranial delivery of CAR T cells elicits superior anti-tumor efficacy compared with intravenous administration. In a multifocal disease model, CAR T cell infusions into the ventricle exhibited possible benefit over intracranial tumor infusions. Overall, these findings help define parameters for the clinical translation of CAR T cell therapy for the treatment of brain tumors.

Scientific Abstract:

T cell immunotherapy is emerging as a powerful strategy to treat cancer and may improve outcomes for patients with glioblastoma (GBM). We have developed a chimeric antigen receptor (CAR) T cell immunotherapy targeting IL-13 receptor alpha2 (IL13Ralpha2) for the treatment of GBM. Here, we describe the optimization of IL13Ralpha2-targeted CAR T cells, including the design of a 4-1BB (CD137) co-stimulatory CAR (IL13BBzeta) and a manufacturing platform using enriched central memory T cells. Utilizing orthotopic human GBM models with patient-derived tumor sphere lines in NSG mice, we found that IL13BBzeta-CAR T cells improved anti-tumor activity and T cell persistence as compared to first-generation IL13zeta-CAR CD8(+) T cells that had shown evidence for bioactivity in patients. Investigating the impact of corticosteroids, given their frequent use in the clinical management of GBM, we demonstrate that low-dose dexamethasone does not diminish CAR T cell anti-tumor activity in vivo. Furthermore, we found that local intracranial delivery of CAR T cells elicits superior anti-tumor efficacy as compared to intravenous administration, with intraventricular infusions exhibiting possible benefit over intracranial tumor infusions in a multifocal disease model. Overall, these findings help define parameters for the clinical translation of CAR T cell therapy for the treatment of brain tumors.